REMARKS

I. Objection Based Upon Claims Containing Non-elected Subject Matter

The Examiner has objected to claims 1-21 for containing non-elected subject matter and has requested the applicants to amend the claims to reflect the elected species, SEQ ID NO:12. Applicants respectfully traverse.

According to M.P.E.P. §809.02(c), an examiner's action subsequent to an election of species should include a complete action on the merits of all claims readable on the elected species and according to M.P.E.P. §809.02(e), whenever a generic claim is found to be allowable in substance, action on the species claims shall thereupon be given as if the **generic** claim were allowed. Thus, if it is determined that the elected species is patentable, it is incumbent upon the Office to search **additional species** that fall within any allowable generic claims. Accordingly, requiring amendment of the claims to included only SEQ ID NO:12 is not proper.

II. Sequence Listing Non-Compliance

A corrected copy of the sequence listing and a computer readable format is enclosed. The specification has been amended to include sequence identification numbers.

III. 35 U.S.C. 103(a) Rejection

Reconsideration is requested of the rejection of claims 1, 2, 12, 13 and 15 under 35 U.S.C. §103(a) in view of Marklund et al.[1] and Kuehn et al.[2]

The primary focus of Marklund et al. was to explore whether horizontal gene transfer events gave rise to the three distinct functional classes of G-adhesins in different strains of *Escherichia coli.*[3] To accomplish this goal, Marklund et al. concentrate on evolutionary relationships between pili gene clusters encoding Class I, Class II or Class III G-adhesins. Recognizing that phylogenetically related strains of *E. coli* normally carry either Class II or Class III, but not Class I, Marklund et al.

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[1]Marklund et al., (1992) Molecular Microbiology 6(16):2225-2242.

[2]Kuehn et al., (1993) Science 262:1234-1241.

[3]Marklund et al., at page 2225.

understandably focus their efforts on strain J96 because it contains an altered pattern of expression having both Class I and Class III. By sequencing and comparing gene clusters of J96 encoding Class I and Class III with patterns of G-adhesin expression in phylogenetically similar strains of *E. Coli*, Marklund et al. conclude that J96 most likely acquired Class I as a result of horizontal gene transfer.

Unlike the disclosure of Marklund et al., claim 1 is not directed toward evolutionary relationships of pili gene expression between strains of *E. coli.* Instead, claim 1 is generally directed toward an **isolated** compound (i.e. peptide) which **inhibits pilus assembly** comprising a mimic of a **chaperone G_1 beta-strand** or a mimic of an **amino terminal motif of a pilus subunit** with at least two alternating hydrophobic amino acid residues or a 10 to 20 residue peptide according to formula I.[4] The peptide compound of SEQ ID NO: 12 exemplifies compounds specified in claim 1. This compound is represented by the following primary structure:

Ser-Asp-Val-Ala-Phe-Arg-Gly-Asn-Leu-Leu

Nowhere do Marklund et al. disclose or suggest an **isolated** compound capable of inhibiting pilus assembly having the structure required by claim 1, as exemplified by SEQ ID NO:12.

According to the Office, however, "the sequence elected [SEQ ID NO:12] is publically known (Marklund et al. has the following peptide, SEQ ID NO: 12 entered into

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[4]For convenience, Formula I as detailed in claim 1 is represented by the structure
Z_1~Z_2-X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-Z_3~Z_4
or a pharmaceutically-acceptable salt thereof, wherein:

Z_1 is R-C(O)-NR- or RRN-; Z_2 is an optional 1 to 5 residue peptide or peptide analog; X_1 is any amino acid residue; X_2 is any amino acid residue; X_3 is a hydrophobic residue or a hydroxyl-substituted aliphatic residue; X_4 is any amino acid residue; X_5 is a hydrophobic residue or Gly; X_6 is a hydrophobic or a hydrophilic residue; X_7 is Gly, an amide-substituted polar residue or a hydrophobic residue; X_8 is any amino acid residue; X_9 is an aliphatic residue; X_{10} is any amino acid residue; Z_3 is an optional 1 to 5 residue peptide or peptide analog; Z_4 is –C(O)OR or –C(O)NRR; each R is independently hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl or (C_6-C_{14}) aryl; each "–" between residues X_1 through X_{10}, Z_2 and X_1 and X_{10} and Z_3 independently represents an amide linkage, a substituted amide linkage or an isostere of an amide linkage; and each "~" represents a bond.

NIH database as accession #: S16400)."[5] This is not correct.[6] The sequence disclosed as accession No. S16400 is **178 amin acid** residues in length where the sequence was **deduced** from the *E. coli papK* gene sequence disclosed in Marklund et al.[7] The peptide disclosed in the cited art, therefore, has not been **isolated** as required by claim 1, but rather, was merely **deduced**. Additionally, while the 10 amino acid residues comprising SEQ ID NO:12 are **embedded** approximately 20 residues from the N-terminus and approximately 140 residues from the C-terminus of the deduced papK protein fragment identified as accession No. S16400, the primary amino acid sequences of SEQ ID NO:12 and that of accession No. S16400 are not the same. Moreover, claim 1 requires an **isolated** compound which **inhibits** pilus assembly. The sequence having accession No. S16400, contrastingly, is a **deduced** sequence of the papK protein. As disclosed in both Marklund et al. and Kuehn et al.,[8] papK is a protein subunit **required** for pilus **assembly**. Accordingly, instead of inhibiting pilus assembly as required by claim 1, the protein having accession No. S16400 would actually **facilitate** pilus assembly.[9]

The defect in the Office's obviousness rejection cannot be overcome by resort to Kuehn et al. The focus of Kuehn et al. was to characterize molecular recognition motifs between chaperones and their protein targets by examining the structural basis of pilus subunit recognition by the PapD chaperone.[10] To accomplish this goal, Kuehn et al. employ a conserved COOH-terminus sequence of a pilus peptide that had previously

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[5]See Paper No. 18 at page 3.

[6]For the Office's convenience, a copy of the sequence registered at the NIH database as accession No. S16400 is enclosed.

[7]See the description for Figure 1 of Marklund et al. which states that the amino acid sequence has been deduced from the gene sequence.

[8]Kuehn et al. at page 1234.

[9]Marklund et al. at Figure 1 on page 2229 and page 2226 (results section), where the sequence identified as accession No. S16400 is identified as a Class I pili-associated G-adhesin.

[10]Kuehn et al., at page 1234.

been shown to interact with PapD.[11] In general, Kuehn et al. disclose that the conserved region within the COOH-terminus sequence has alternating hydrophobic-hydrophilic residues and a tyrosine and a glycine residue at positions 2 and 14 from the COOH-terminus, respectively.[12] By comparing results from both structure and function analysis, Kuehn et al. conclude that chaperone residues Arg^{8} and Lys^{112} are crucial for the interaction of PapD with its target protein.

In contrast to the disclosure of Kuehn et al., claim 1 is not directed toward molecular recognition motifs between chaperones and their protein targets. Nowhere do Kuehn et al. disclose or suggest an **isolated** compound capable of inhibiting pilus assembly having the structure required by claim 1, as exemplified by SEQ ID NO:12.

The Office, however, asserts that Kuehn et al. disclose a method to inhibit pilus subunit assembly. In particular, the Office relies on the last paragraph of Kuehn et al which states:

> ...the mode of chaperone binding described in this article actually presents a "snapshot" of a process fundamental to Gram-negative pathogens. The molecular details of chaperone-adhesin interaction and optimization...**may lead** to the design of high affinity synthetic inhibitors which would prevent pilus assembly...[13]

At most, this statement is of the type that gives only general guidance. It simply reflects the authors' recognition that an understanding of how chaperones interact with their protein targets **may** lead to the **development** of peptides capable of disrupting this interaction (i.e. an interaction necessary for pilus assembly). By way of example, it is analogous to an author suggesting a concept for an enhanced cancer treatment by selectively directing chemotherapeutic agents to only cancerous cells, but then not providing any guidance as to how either the agents would be directed to only the cancerous cells or even what the agents would comprise. Nowhere do Kuehn et al. disclose or suggest any peptides or even features of peptides that would effectively

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[11]Kuehn et al., at page 1235.

[12]Kuehn et al., at page 1235.

[13]Kuehn et al., at page 1240.

function to disrupt the interaction of a chaperone with its target protein (i.e. to inhibit pilus assembly).

According to the Office, it would have been obvious for a skilled artisan to combine Marklund et al.'s supposed disclosure of SEQ ID NO:12 (i.e. a protein that does disrupt pilus assembly) with Kuehn et al.'s disclosure of disrupting chaperone/target protein interaction as a means to inhibit pilus assembly in order to arrive at the compound of claim 1. Not only is this assertion unsupported by any citation to any art of record, it is inconsistent with the collection of art cited by the Office. Marklund et al., as detailed above, do not disclose isolated SEQ ID NO:12. Rather, they disclose 10 amino acids in a row having the same amino acids as SEQ ID NO:12, but **embedded** in an amino acid sequence that was **deduced** from a non-isolated gene from *E.coli* DNA. Nothing in Marklund et al. would have led a skilled artisan to select the particular 10 amino acids comprising SEQ ID NO:12 from the much longer sequence disclosed. Moreover, the sequence disclosed by Marklund et al., when not taken out of context as the Office has done, performs a diametrically different function compared to SEQ ID NO:12 as it pertains to pilus assembly. The Marklund et al. sequence cited by the Office **causes** pilus assembly, SEQ ID NO:12, as required by claim 1, **inhibits** pilus assembly. Assuming, *aguendo*, that Kuehn et al. do disclose a concept of a means to inhibit pilus assembly, they provide no disclosure or suggestion as to how a skilled artisan is to use or reduce their concept to practice. Contrary to the Office's assertion, a skilled artisan would not select the sequence disclosed in Marklund et al. containing SEQ ID NO. 12 and employ it in the rather vague method to inhibit pilus assembly disclosed in Kuehn et al. Because if he or she did, pilus assembly would not be inhibited, it would be facilitated. Nowhere does the cited art, when taken singly or collectively, disclose or suggest the isolated compound of claim 1, as exemplified by SEQ ID NO:12, to inhibit pilus assembly.

If anything, the art cited **teaches away** from the compound of claim 1. The entire focus of Kuehn et al. is the characterization of the interaction of **a conserved C-terminus portion** of a pilus protein with the chaperone, **PapD**. Kuehn et al. disclose portions of the C-terminus region that are highly conserved across *E. coli* species and two residues (i.e. Arg^{8} and Lys^{112}) necessary for PapD to function as a chaperone. Moreover, the cited art discloses areas within the C-terminus region that contact the

chaperone and the importance of chaperone/target protein interaction in the process of pilus subunit assembly. Kuehn et al. also focus solely on the chaperone PapD. They do not disclose or suggest chaperone G_1 or a mimic thereof. Claim 1 is directed toward a compound that is a mimic of a chaperone G_1 beta-strand or a mimic of an **amino terminal motif of a pilus subunit**. Based on the disclosure of Kuehn et al., a skilled artisan would concentrate on the **carboxy-terminal end** of a pilus subunit to develop an inhibitor of pilus assembly as opposed to the **amino terminal** recited in claim 1.[14] A skilled artisan empowered with the collective art of record, therefore, would not arrive at the compound of claim 1 without the disclosure of the Applicants' patent application.

Unable to establish a *prima facie* case of obviousness, it appears that the Office has effectively slipped into an improper "obvious to try" analysis, informed by hindsight which Applicants' disclosure affords. But the courts have consistently held that the test for a *prima facie* case of obviousness is not whether an invention is obvious to try.[15] Instead, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references, and there must be some reasonable expectation of success. For all the reasons detailed above, the Office has not met this legal standard.

For the foregoing reasons, the Office has failed to establish that claim 1 is *prima facie* obvious in view of Marklund et al., and Kuehn et al. Moreover, claims 2, 12, 13 and 15, which depend from claim 1, are likewise patentable over these references for the reasons stated with respect to claim 1. New claim 136, which also depends from claim 1 and is limited solely to a compound consisting of SEQ ID NO:12, is also patentable over the cited art for the reasons detailed with respect to claim 1.

IV. Conclusion

In light of the foregoing, Applicants request withdrawal of the final rejection, entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of

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[14]Kuehn et al. do mention in passing (at page 1239) that other regions of a pilus subunit may be involved in chaperone binding, including the amino terminal. But this is mentioned only in one line of a 8 page paper and is only mentioned as a possibility.

[15] See In re O'Farrell, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988).

the claims. The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Replace the fifth paragraph on page 10 with:

Fig. 3B is a depiction of the sequence alignment of P-pilus subunits (PapA **(Seq. ID No: 57)**, PapK **(Seq. ID No: 58)**, PapE **(Seq. ID No: 59)**, and PapF **(Seq. ID No: 60)**). The secondary structural elements of PapK are indicated above the aligned sequences. Residue numbers of PapK are indicated above the PapK sequence. The remarkable conservation of structurally and functionally important residues strongly indicates that all pilins have structures similar to PapK.

Replace the sixth paragraph on page 10 with:

Fig. 3C is a depiction of the secondary structure definition of PapD **(Seq. ID No: 61)**. Residue numbers are indicated above the sequence, while secondary structural elements are indicated below it.

Replace the first paragraph on page 12 with:

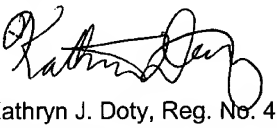
Fig. 8A depict the amino acid sequences of type 1 pilus subunits (FimA **(Seq. ID No: 62)**, FimF **(Seq. ID No: 63)**, FimG **(Seq. ID No: 64)**, FimH **(Seq. ID No: 65)**). The end of the mannose binding lectin domain and the start of the pilin domain in FimH are indicated by vertical arrows above the sequences. Type 1 pilin subunits (FimA, FimF, FimG) were aligned with the pilin domain of FimH using Clustal W and manually adjusted to minimize gaps in secondary structure elements. Gaps in the alignment are indicated by dots. Sequence numbering for FimH starts at position 22 in the pre-protein. Residues involved in chaperone binding are indicated by an open circle above the residue. Residues in the carbohydrate binding pocket are boxed. A large box marks the NH_2-terminal extensions in the pilin subunits. The conserved b-zipper motif found in all pilin subunits corresponds to the F beta-strand. Limits and nomenclature for secondary structure elements are shown below the sequence.

IN THE CLAIMS

Claim 136 has been added.

If there are any additional charges in this matter, please charge Deposit Account No. 19-1345.

Respectfully submitted,



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